嘌呤霉素敏感的氨肽酶结构与功能研究进展

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摘要: 嘌呤霉素敏感的氨肽酶 (puromycin-sensitive aminopeptidase, PSAP) 是一种M1氨肽酶 (M1 aminopeptidases), 具有对嘌呤霉素敏感的特性。其结构包括N端底物结合序列GAMEN、酶活中心HEXXH(X)$_{18}$E基序以及C端ERAP-1样超家族 (ERAP like superfamily) 结构域。作为M1型氨肽酶中的重要亚型, PSAP由定位于17q21.32的基因*NPEPPS*编码, 全长为919个氨基酸。PSAP广泛分布于人体各组织, 在脑中表达最高, 其次是心脏和骨骼肌。同时, PSAP也在肝脏、肾小管上皮、小肠和大肠上皮以及胃上皮细胞中表达。通过其水解活性, PSAP可以清除一些毒性蛋白聚集体, 如微管相关蛋白Tau、多聚谷氨酰胺 (poly Q) 及铜锌超氧化物歧化酶 (SOD1) 等, 参与阿尔茨海默症、亨廷顿舞蹈病、肿瘤等疾病的发生发展过程。现有PSAP酶活抑制剂包括bestatin、amastatin、leuhistin、actinonin和嘌呤霉素等, 其中一些已经成药或者正在进行临床试验。本文总结了M1氨肽酶特别是PSAP的生物学功能、结构和相关药物研究进展, 旨在为深入研究PSAP的结构、功能及靶向药物的开发提供依据。

关键词: M1氨肽酶; 嘌呤霉素敏感的氨肽酶; 结构与功能; 疾病; 抑制剂

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Advances on research of structure and function of puromycin sensitive aminopeptidase

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Abstract: Puromycin-sensitive aminopeptidase (PSAP) belongs to the M1 family of aminopeptidases, characterized by the N-terminal substrate binding sequence GAMEN, the enzyme activity center HEXXH(X)$_{18}$E motif, and the C-terminal ERAP-1-like superfamily structural domain. Encoded by the gene *NPEPPS* located at 17q21.32, PSAP consists of 919 amino acids and is widely distributed throughout the human body, with the highest expression in the brain, followed by the heart and skeletal muscle. It is also found in the liver, renal tubular epithelium, small intestine, large intestine epithelium, and gastric epithelial cells. PSAP primarily relies on its aminopeptidase hydrolytic activity to remove toxic protein aggregates such as Tau, poly Q, and Cu, Zn-superoxide dismutase 1, making it an important factor in the development of diseases such as Alzheimer's disease, Huntington's chorea, and tumors. Existing PSAP inhibitors include bestatin, amastatin, leuhistin, actinonin, and purinomycin, some of which are already available or in clinical trials. This review provides an overview of the structural and biological functions of M1 family aminopeptidases, with a focus on PSAP, to facilitate further research and targeted drug development.

Key words: M1 aminopeptidase; puromycin-sensitive aminopeptidase; structure and function; disease; inhibitor

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肽酶 (peptidase) 是一种能够水解肽链的酶。它们可以分为两大类型, 即内肽酶 (endopeptidases) 和外肽酶 (exopeptidases)。其中内肽酶是一种破坏蛋白质分子内肽键的蛋白质切割酶。外肽酶是一种催化末端肽键断裂的酶, 它可以将末端单个肽键从蛋白质分子中去除。外肽酶根据其剪切肽链末端为氨基端或羧基端又可分为氨肽酶 (aminopeptidases) 和羧基肽酶 (carboxypeptidases)。氨肽酶主要催化多肽或者蛋白N-端游离氨基酸残基的水解[1,2]。大多数氨肽酶都属于金属氨肽酶, 其活性需要1～2个金属离子的辅助, 如Zn^{2+}、Mn^{2+}、Co^{2+}, 其中大多数氨肽酶是Zn^{2+}依赖性的。部分氨肽酶需要两种不同的金属离子辅助, 其中一个金属离子起催化作用, 另一个金属离子负责活性的调节[3]。氨肽酶广泛分布于动物、植物、细菌和真菌中[4]。大多数定位于胞质、微粒体或膜中, 部分会分泌到胞外[1,5,6]。氨肽酶参与众多的生理过程, 如氨基酸调节[7]、信号肽的修饰[8]、细胞周期调控[9,10]、肿瘤生长及血管生成、蛋白质成熟与稳定维持等[11-14]。

氨肽酶根据催化方式不同可分为3大类, 分别是金属氨肽酶、半胱氨酸氨肽酶和丝氨酸氨肽酶。根据金属离子所在的位置又可以将金属氨肽酶分为M1和M2氨肽酶。M1氨肽酶 (M1 aminopeptidases) 包含12种人源氨肽酶 (图1), 其活性主要依赖于Zn^{2+}[15]。M1氨肽酶具有两条高度保守的基序: $HEXXH(X)_{18}E$和GXMEN。Zn^{2+}结合位点由组氨酸和谷氨酸组成, 分别位于两条反平行的螺旋上[16]。研究表明, M1氨肽酶的活性和Zn^{2+}对水分子的活化有关[16]。GXMEN基序主要用于识别底物N-端游离的氨基酸[17]。M1氨肽酶广泛分布于各种生物中, 参与细胞形态维持、生长发育及防御等多种细胞活动[18]。嘌呤霉素敏感的氨肽酶 (puromycin-sensitive aminopeptidase, PSAP) 具有M1氨肽酶特有的活性催化中心, 因此将其归属于M1氨肽酶。本文将就M1氨肽酶特别是PSAP的生物学功能、结构及相关药物研究进展进行综述。

1 M1氨肽酶成员简介

人源M1氨肽酶主要包含以下12种 (表1)[19-38]。根据其亚细胞定位的不同可分为膜结合型和非膜结合型。其中绝大多数的M1氨肽酶含有跨膜结构域, 定位在细胞膜及细胞器膜上。氨肽酶N (aminopeptidase N, AP-N)、AP-A和胰岛素调节的氨肽酶 (insulin regulated aminopeptidase, IRAP) 定位于细胞膜, AP-Q、促甲状腺激素释放激素降解酶 (thyrotropin releasing hormone degrading enzyme, THR-DE)、内质网氨肽酶1 (endoplasmic reticulum aminopeptidase 1, ERAP1) 和ERAP2定位于细胞器膜, AP-B及IRAP分泌至胞外, 白三烯A4水解酶 (leukotriene A4 hydrolase, LTA-4H)、AP-O和PSAP分布于胞浆及细胞核中。

1.1 AP-N

AP-N又称CD13, 是一种广泛存在于人体各种组织和细胞中的酶, 由967个氨基酸组成, 具有一个N-端胞质结构域、一个跨膜部分和一个包含活性位点的胞外段[39], 可加工胃肠道吸收的多肽、神经肽及多种趋化因子, 如血管紧张素III、凝血素、激肽、生长抑素等[22], 并参与肿瘤的血管生成和转移[39]。此外, AP-N还可以作为细胞膜受体参与主要组织相容性复合物II (MHC II) 对多肽的识别过程[40], 并是人类冠状病毒229E

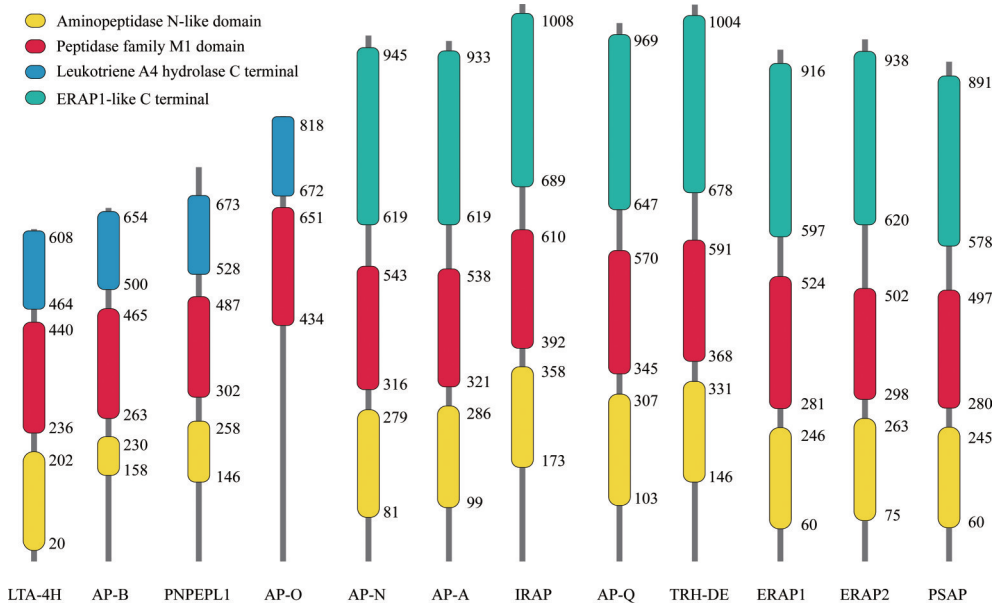

Figure 1 Comparison of structural domains among members of the M1 aminopeptidase family

Table 1 Human M1 aminopeptidase family. TRH-DE: Thyrotropin releasing hormone degrading enzyme; AP: Aminopeptidase; RNPEPL1: Arginyl aminopeptidase like 1; LTA-4H: Leukotriene A4 hydrolase; ERAP: Endoplasmic reticulum aminopeptidase; IRAP: Insulin regulated aminopeptidase; PSAP: Puromycin-sensitive aminopeptidase

Protein name	Gene name	Subcellular localization	Function and related disease
AP-B	*RNPEP*	Secreted	Removes arginine and/or lysine residues from the N-terminus of several peptide substrates; Haverhill fever, subacute bacterial endocarditis[19]
AP-Q	*LVRN*	Membrane	Regulate biological activity of key peptides at the embryo-maternal interface; lacrimal gland carcinoma and lacrimal gland adenoid cystic carcinoma[20]
TRH-DE	*TRHDE*	Membrane	It specifically cleaves and inactivates the neuropeptide thyrotropin-releasing hormone; thyroid hormone resistance, generalized, autosomal dominant and developmental and epileptic encephalopathy 2[21]
AP-N	*ANPEP*	Cell membrane	It is involved in the final digestion of peptides generated from hydrolysis of proteins by gastric and pancreatic proteases; a receptor for the HCoV-229E alpha coronavirus as well as other non-human coronaviruses, gastroenteritis and B-lymphoblastic leukemia/lymphoma[22]
AP-A	*ENPEP*	Cell membrane	It can cleave N-terminal acidic residues from angiotensin II; choriocarcinoma and retinitis pigmentosa 71[23,24]
RNPEPL1	*RNPEPL1*	Unknown	Broad specificity aminopeptidase. It preferentially hydrolyzes an N-terminal methionine, citrulline or glutamine; type 2 diabetes mellitus[25]
LTA-4H	*LTA4H*	Cytoplasm	Possessing dual activity as both a hydrolase and an aminopeptidase, promoting the production of leukotriene B4; associated with asthma and palatal cancer[26,27]
AP-O	*AOPEP*	Nucleolus/cytoplasm	Aminopeptidase activity; dystonia 31 and tracheoesophageal fistula with or without esophageal atresia[28]
ERAP2	*ERAP2*	ER membrane	The N-terminal cleavage of MHC class I molecules for antigen presentation; spondylitis and eclampsia[29-31]
ERAP1	*ERAP1*	ER membrane	Involved in trimming HLA class I-binding precursors, promoting antigen presentation and cleaving the N-terminal amino acids of angiotensin II; peeling skin with leukonychia, acral punctate keratoses, cheilitis, and knuckle pads and behcet syndrome[32-34]
IRAP	*LNPEP*	Cell membrane/ secreted	Cleaving the N-terminal amino acids of substrates, especially those before cysteine and leucine residues; placental site trophoblastic tumor and birdshot chorioretinopathy[35]
PSAP	*NPEPPS*	Nucleolus/cytoplasm	Cleaving the N-terminal amino acids of substrates to degrade enkephalins; frontotemporal dementia and Alzheimer's disease[36-38]

(HCoV-229E) 的识别受体之一[22]。目前有多个研究团队在开发AP-N抑制剂, 以研究其在肿瘤生长和转移、病毒感染、肿瘤血管梗死等方面的作用[41-45]。

1.2 AP-A

AP-A是一种II型膜结合蛋白, 由957个氨基酸组成。它包含一个短的N-端胞内结构域、一个单通道跨膜锚、一个小柄和一个大的C-端胞外结构域[23]。AP-A主要以二聚体的形式结合于细胞膜[46]。AP-A具有特异性水解能力, 可以释放多肽或蛋白质的N-端谷氨酸或天冬氨酸残基[47]。AP-A广泛分布于各类组织中, 但在脑、肠道和肾脏的刷状边缘的含量多于其他组织[48]。研究表明, AP-A在中枢血压调节中扮演重要角色。它可以将血管紧张素II特异性转化为血管紧张素III, 参与高血压的维持。这种特异性转化能力取决于Ca^{2+}浓度的生理条件调节[23,24,49]。

1.3 IRAP

IRAP是一种II型膜结合蛋白, 由1 025个氨基酸构成。它具有一个由109个氨基酸组成的N-端胞质内结构域和一个由893个氨基酸组成的胞外区, 活性中心位于胞外区[50]。IRAP最初在脂肪和肌肉细胞中被发现, 与葡萄糖转运体GLUT4共定位于特殊的囊泡中。这些囊泡在胰岛素受体刺激下将会转位至细胞膜, 促进细胞的葡萄糖摄取[51]。后来, IRAP在脑中及胎盘中被分离出来, 并发现其可以对环肽 (如催产素和加压素) 进行特异性切割。同时, IRAP对血管紧张素IV及其受体LVV-haemorphin 7具有高亲和力。这些多肽均被报道与认知障碍相关, 因此IRAP被认为是治疗认知障碍的潜在靶点[52-55]。

1.4 ERAP1/2

ERAP1/2属于催产素酶亚家族, 在人体组织中广泛表达。它们在心脏、胎盘以及脾脏中的表达水平较高[56]。ERAP1是一种多功能酶, 可将多肽水解至最佳长度, 便于组织相容性复合体I类分子 (MHC I) 呈递[57,58]。生化研究发现, ERAP1活性位点更容易与9～15个氨基酸的寡肽结合, 结合后水解N-端氨基酸残基。ERAP2与ERAP1的结构相似, 二者都能与MHC I类分子结合并调控其表达, 参与抗原递呈过程[32,59]。全基因组关联分析表明, ERAP1/2与强直性脊柱炎高度相关[60]。ERAP1和ERAP2的常见突变与多种人类疾病 (病毒感染、自身免疫病和癌症) 相关[61]。

1.5 LTA-4H

LTA-4H是一种具有氨基肽酶和环氧化合物水解酶活性的双功能酶[62]。LTA-4H由625个氨基酸构成, 折叠为3个结构域, 分别为N-端、催化中心和C-端, 这些结构域以扁平的三角形排列, 在它们之间形成一个深深的裂缝, 活性中心位于域间裂缝的底部[63]。LTA-4H在许多细胞中均有表达, 尤其是在许多免疫细胞中。LTA-4H的活性催化中心与脂肪酸底物白三烯A4 (LTA4) 结合, 使其发生环氧化物水解反应, 将LTA4转化成LTB4, 参与机体的炎症免疫反应、宿主抵抗感染、血小板激活因子诱导的休克及脂质内稳态等过程[62,63]。

综上所述, M1氨肽酶是一类多聚体酶, 通常与细胞膜或者细胞器膜结合。其结构通常包括一个N-端的短基序、一个跨膜的柄及具有催化活性中心的C-端结构域[18] (图1)。由于M1氨肽酶活性中心形成了底物结合口袋, 因此从药物设计角度看, 它的抑制剂开发具有较好的可行性。随着对M1氨肽酶在各种生理过程中功能的研究日益深入, 其抑制剂的开发也逐渐受到重视。

2 PSAP

2.1 PSAP的结构

PSAP于1980年首次被报道。越来越多的研究表明, 该氨肽酶在毒性蛋白清除、免疫、肿瘤治疗中发挥重要的作用, 因此可能成为相关疾病治疗的重要靶点。

1980年, Hersh等[64]从牛、猴子或大鼠脑中提取了一种新的氨肽酶, 该酶可以水解内啡肽N端的酪氨酸。次年, 该团队[65]发现此酶对嘌呤霉素敏感。在随后的30多年里, 研究者们对PSAP进行了详细的探究, 包括其基因定位、蛋白结构域、疾病相关性等方面。

PSAP由基因*NPEPPS*编码, 包含26个外显子和22个内含子, 定位于17q21.32, 长度约为40 kb[66-68]。PSAP全长919个氨基酸, 在人体内分布十分广泛, 肝脏、肾小管上皮、小肠和大肠上皮、胃上皮细胞和肺泡等组织中均有表达, 在心脏、脑及骨骼肌中的含量较其他组织更多[69,70]。在细胞中, PSAP通常定位于细胞质和细胞核中, 在大脑中存在膜结合形式。在有丝分裂过程中, PSAP会与纺锤体结合, 参与调节有丝分裂过程[5,69]。

PSAP含有N-端M1 APN-Q样结构域 (M1 APN-Q like domain, 61～499位氨基酸), 由多个β-片层样结构组成, 其中包含底物结合序列GAMEN及酶活中心HEXXH(X)$_{18}$E基序; C-端ERAP-1样超家族 (ERAP1 superfamily) 结构域位于579～891位氨基酸, 该结构域的16个α螺旋组成8个热样重复结构, 这样的结构在蛋白质折叠过程中会形成一个巨大的凹面, 凹面朝向氨肽酶的活性中心, 将活性中心包裹于内, 核定位信号也包含其中。通过对Alphafold预测的蛋白结构进行分析发现, PSAP 1～241位氨基酸构成的β-片层结构具有寡聚化倾向, 这与M1氨肽酶的特点相符; PSAP整体结构类似于一只手, 酶活中心区域被虚握于手心的位置, 相较其他的同源酶更加暴露, 底物结合基序口袋直径更大 (图2)。

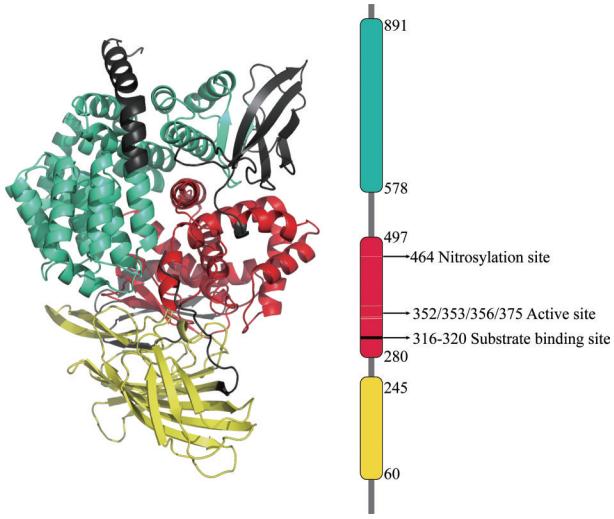

Figure 2 The predictive structure of PSAP

PSAP蛋白的修饰报道较少, 仅有464位的硝基化修饰。关于突变对PSAP功能影响的报道较少, 通过预测发现突变309位的谷氨酸会导致PSAP失去酶活, 转变成无酶活结合蛋白, 突变394位点的酪氨酸将会导致酶活大幅减弱[71]。

2.2 PSAP的生物学功能

已有研究表明, PSAP可以水解强啡肽和脑啡肽等生理性内源肽, 从而促进这些肽在脑中的降解[38]。最近的研究显示PSAP在毒性蛋白清除、免疫和肿瘤治疗等方面有一定的功能。

在毒性蛋白清除方面, 研究人员发现PSAP可以参与清除易聚集的蛋白质, 如多聚谷氨酰胺序列 (polyQ)。哺乳动物蛋白酶体无法切割polyQ序列, 而PSAP是唯一一种能够消化polyQ序列的胞质酶, 并且PSAP也能通过促进polyQ的自噬清除, 防止其在细胞中的累积[72]。此外, PSAP还能够靶向病理性聚集的铜锌超氧化物歧化酶 (SOD1) 蛋白进行降解。在肌萎缩侧索硬化症 (amyotrophic lateral sclerosis, ALS) 中, SOD1蛋白的累积是导致神经元细胞死亡的一个重要因素。通过水解SOD1, PSAP降低其在细胞内的丰度, 从而可能对ALS的病理过程起到延缓和改善的作用[73]。在阿尔茨海默症 (AD) 的研究中, PSAP的过表

达能够减少Tau蛋白的聚集。具有神经毒性的过度磷酸化的Tau蛋白的积累是AD及与Tau蛋白相关的神经退行性疾病的主要病理标志。研究人员构建BAC-PSA/NPEPPS转基因小鼠并将其与Tau^{P301L}神经变性小鼠模型进行杂交。结果显示, 杂交后该小鼠模型出现了麻痹延缓的趋势, 运动神经元计数也显著提升, 机制研究表明PSAP过表达可以阻止过度磷酸化Tau蛋白的积累, 从而产生神经保护作用[36,74]。此外, 一些研究者通过利用嘌呤霉素给药处理在细胞水平也证实了PSAP参与了Tau蛋白的水解[37]。目前, 普遍认为PSAP通过其氨肽酶的活性, 在神经元细胞中减弱疾病相关蛋白的积聚, 最终保护神经元细胞, 缓解神经退行性疾病的发展。

在免疫调节方面, PSAP可以加工树突状细胞中的多肽, 限制MHC I类分子的抗原呈递过程, 但不影响$CD8^+$T细胞的免疫应答[75]。后续研究表明, PSAP可以催化蛋白质酶衍生肽段的加工, 由ERAP1和ERAP2修剪抗原肽, 然后被修饰的抗原肽用于MHC I类分子的递呈。一系列全基因组关联研究表明, PSAP可能涉及多种免疫介导的疾病, 如强直性脊柱炎、银屑病、贝氏病、炎症性肠病和1型糖尿病等[71]。然而, 目前为止尚未有详细的研究描述PSAP在这些疾病中的具体作用机制, PSAP抑制剂在治疗此类疾病中的研究仍然是空白。

PSAP在肿瘤的治疗和诊断方面也具有重要作用。如PSAP可以作为结直肠癌肿瘤标志物, 用于肿瘤的诊断及预后[76]。PSAP在肺癌中高表达, 因此研究人员设计了一种依赖于PSAP水解酶活性的荧光探针—谷氨酰胺−丙氨酸-2-甲氧基硅罗丹明 (QA-2Omesir), 其可以快速识别肺癌微小病变灶并准确界定肿瘤边界, 从而提高手术效果[77]。研究人员发现敲除PSAP可以降低人前列腺癌PC-3细胞的增殖、迁移和侵袭, 并减少基质金属蛋白酶-9 (MMP-9) 的分泌和表达[78]。PSAP还可以和体积调控阴离子通道 (volume regulated anion channel, VRAC) LRRC8A结合, 降低细胞对顺铂的吸收, 这可能是顺铂在膀胱尿路上皮癌中产生耐药的原因之一[79]。此外, 基于嘌呤霉素设计改造的PSAP酶活抑制剂在体外对白血病细胞系显示出良好的抑制活性[80]。在肿瘤免疫方面, PSAP与肿瘤特异性细胞毒性T淋巴细胞 (cytotoxic T lymphocytes, CTL) 表位的产生和自噬降解相关, 该表位在白血病和胰腺癌细胞上表达, 而不在正常的成纤维细胞和EBV转化的B淋巴母细胞中表达[81]。

在生长发育方面, PSAP在有丝分裂和减数分裂期间发挥重要作用, PSAP及同源酶加工微小肽段, 促进蛋白质运输和信号传导的过程, 直接或间接影响细胞周期[9,69]。敲除PSAP可导致C2C12成肌细胞的细胞周期进程受损, 细胞阻滞于G2/M期。此外, 在PSAP基因敲除的成肌细胞诱导成肌分化后, 经常出现多核圆形肌管和细胞极性损坏, 表明PSAP对成肌细胞生长阶段的增殖和分化阶段的细胞极性及肌管伸长有重要作用[82]。在小鼠中, PSAP敲除的品系存活胚胎数减少, 导致产仔数减少, 并且幼仔体型更小且不育, 提示PSAP在生长发育方面具有重要的作用[83,84]。

除上述研究之外, 最新研究表明PSAP是肝脏脂代谢的一个关键调节剂。PSAP通过抑制NF-E2相关因子2 (nuclear factor erythroid 2-related factor 2, NRF2) 泛素化, 稳定NRF2蛋白表达, 实现其抗氧化功能。因此, PSAP可能是治疗非酒精性脂肪性肝病 (NAFLD) 的潜在生物标志物和治疗靶点[85]。此外, PSAP还与焦虑及疼痛的产生具有较强的相关性[86]。

以上研究表明, PSAP在不同的疾病中扮演着不同角色。在某些疾病中, PSAP过表达有助于疾病的减轻, 在另一些疾病中, PSAP敲除有助于疾病的减轻。这提示PSAP在不同生理病理环境中和不同底物结合可能会发挥不同功能。因此, 系统解析PSAP的底物种类、规律及作用方式是未来进一步的研究方向。

2.3 PSAP抑制剂研究现状

目前的研究表明, PSAP在毒性蛋白的清除、免疫相关疾病和肿瘤治疗方面发挥着重要作用。为此, 研究人员正在逐步开发PSAP的抑制剂。现有PSAP酶活抑制剂包括bestatin、amastatin、leuhistin、actinonin和嘌呤霉素等。

2.3.1 Bestatin 乌苯美司 (bestatin) 是一种二肽广谱氨肽酶抑制剂, 可抑制细胞LTA-4H、AP-B和AP-N等氨肽酶的活性。该化合物于1976年由Kayaku从链霉菌中分离出来, 并获批用于治疗急性非淋巴细胞白血病。目前, 在美国该药物正在进行临床II期临床试验, 用于治疗肺动脉高压和淋巴水肿。研究表明, bestatin还可用于急性和慢性粒细胞白血病、肺癌和鼻咽癌等疾病的辅助治疗, 并对高胆固醇血症有治疗作用。Bestatin的成功开发提示氨肽酶具备药物靶标的属性。

2.3.2 Amastatin 阿马他汀 (amastatin) 是一种可逆的竞争性广谱氨肽酶抑制剂, 从链霉菌ME 98-M3中分离得到。它可以抑制亮氨酰氨肽酶、丙氨酰氨肽酶、细菌亮氨酰氨肽酶、催产酶、谷氨酰氨肽酶及PSAP等酶活性[87]。然而, 它对氨肽酶B没有抑制作用。研究表明, 在体内阿马他汀可以增强催产素和加压素对中枢神经系统的作用, 同时抑制强啡肽A和其他内源性

肽的降解[88,89]。目前尚未进入临床。

2.3.3 PAQ-22 PAQ-22母核来源于PIQ-22, 最初被设计用于抑制AP-N。同时, 它也是一种强效的PSAP酶活抑制剂。然而由于其化学结构不稳定, 易在四氢异喹啉环上苄亚甲基的位置氧化生成三羰基衍生物。因此, 对其结构进行修饰并开发了化学稳定的PAQ-22[90]。酶动力学研究显示, PAQ-22是PSAP的一种非竞争性抑制剂[91]。目前, 只有关于其对细胞侵袭具有抑制作用的报道。

2.3.4 Artenimol 双氢青蒿素 (artenimol) 常被用来治疗无并发症的恶性疟原虫感染。作为青蒿琥酯的代谢物, artenimol对炎症性肺部疾病具有较好的治疗作用。非靶向蛋白质组学研究发现, PSAP是artenimol的一个结合蛋白, 但其对PSAP活性及功能的影响尚未有研究[92]。

2.3.5 CHR-2797 CHR-2797又称tosedostat, 是M1氨肽酶的抑制剂, 主要作用于PSAP和LTA-4H。在多种癌症模型中显示出药理活性, 包括急性髓系白血病、胰腺癌、多发性骨髓瘤等。Tosedostat目前已进入II期临床研究, 用于治疗急性髓系白血病[93]。关于其抑制PSAP等M1氨肽酶的作用方式及抗肿瘤机制尚未有报道。

3 总结和展望

综上所述, PSAP是一种锌依赖性金属氨基肽酶, 具有重要的生物学功能, 包括调节游离氨基酸的细胞浓度、细胞内蛋白质的加工和周转、调节血管生成和免疫细胞功能、促进肿瘤生长和神经系统疾病等。已有研究显示在不同的疾病条件下, PSAP会发挥促进或者缓解疾病的作用。尽管关于PSAP生物学功能的报道已有不少, 但相对来说, 其机制的研究还相对浅显, 如PSAP的底物有哪些, 通过调控这些底物, PSAP将发挥何种功能等都值得进一步研究。PSAP详细生物学功能及其生理病理作用的阐明将为未来的药物开发提供重要的指导意义。

目前, 针对PSAP药物开发取得的进展也较为缓慢。以bestatin和PAQ-22为例, 目前的PSAP抑制剂都存在毒性大、特异性低等缺陷。造成这些缺陷的原因可能有以下几点: 首先PSAP的晶体结构尚未解析, 其次PSAP发挥酶活的具体机制尚不明确。这些问题均会阻碍PSAP抑制剂或激活剂的开发。利用多组学技术包括蛋白质组学和代谢组学识别和表征PSAP的底物, 开发高通量筛选体系, 将有助于选择性PSAP抑制剂的开发。同时利用特异性的PSAP抑制剂作为探针, 又将助力于PSAP在各种疾病包括神经系统疾病、免疫炎症和肿瘤等作用机制的阐明。

总的来说, 对PSAP的进一步研究可以更好地理解其生物学功能, 并开发出可能对一系列疾病具有治疗潜力的靶向药物。

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